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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	**Application No.** 10/501,628	**Applicant(s)** MARTIN ET AL.	
	Examiner Kimberly A. Makar, Ph.D.	**Art Unit** 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 22 May 2007.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-9,13,15,18-25,58,97,125 and 262-300 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-9,13,15,18-25,58,97,125 and 262-300 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 15 July 2004 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 11/22/04;01/15/03;05/08/07.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group I in the reply filed on 4/17/07 is acknowledged.

2. Claims 34, 159, 172-173, 180,192-194,203, 213-214 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/17/07.

3. The cancellation of claims 34, 159, 172-173, 180,192-194,203, 213-214, and addition of claims 262-300 by applicant in the reply filed 4/17/07 is acknowledged.

4. For the purposes of prosecution, the following is defined:

5. ***Hybridoma***:

6. A somatic cell hybrid formed by fusion of normal lymphocytes and tumor cells; the resulting hybridoma cells will produce the same secretion as the normal parent cells and proliferate indefinitely in culture like the parent tumor cells.

B cell hybridoma: A hybridoma formed by the fusion of antibody-secreting B lymphocytes and nonsecretory myeloma cells; used in the production of monoclonal antibodies.

T cell hybridoma: A hybridoma formed by the fusion of T lymphocytes and myeloma cells, used particularly in the production of T lymphocyte-derived lymphokines. hybridoma. (2003). In Dorland's Illustrated Medical Dictionary. Retrieved August 11, 2007, from http://www.credoreference.com/entry/4173977hybridoma. (2003). In Dorland's Illustrated Medical Dictionary.

7. ***Monoclonal Antibody***:

8. An antibody produced by a single clone of cells. A monoclonal antibody is therefore a single pure type of antibody. Monoclonal antibodies can be made in large quantities in the laboratory and are a cornerstone of immunology. Monoclonal antibodies are increasingly coming into use as therapeutic agents. monoclonal

antibody. (2003). In Webster's New World™ Medical Dictionary. Retrieved August 11, 2007, from http://www.credoreference.com/entry/2437716monoclonal antibody. (2003).

Oath/Declaration

9. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Claim Objections

10. Claims 18 and 19 are objected to because of the following informalities: Claims 18 and 19 are missing the hyphen between the numbers 1 and 17. And should recite: The method of any one of claims "1-17." Additionally, claims 18 and 19 are dependent upon claims cancelled claims 10-12, 14, and 16-17. Appropriate correction is required.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 6-9, 262 – 265, 294-297, and 299-300 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. Claims 6-9 refer to the amount of polyA mRNA of "the gene" comprising a specific amount of total polyA mRNA in the cell in claim 1. Claim 1 has two distinct

genes: a gene into which a mutation is being induced, and a transgenic AID gene. It is unclear which gene claims 6-9 refer to. The methodology can change drastically depending upon which gene that claim is directed to, as it may reflect how much of the mutated gene is mutated by expressing the AID transgene if there is more gene to mutate (more gene to mutate = more mutated gene, irrespective of AID levels), or does the amount of mutation change depending upon how much AID gene is expressed (more AID gene = more mutation?). A skilled artisan would be unable to determine the metes and bounds of the claimed invention,

14. Claims 262-265 refer to "the method of claim 1, wherein the gene is..." Claim 1 has two distinct genes: a gene into which a mutation is being induced, and a transgenic AID gene. It is unclear which gene claims 262-265 refer too. The methodology can change drastically depending upon which gene that claim is directed to, as for example if claim 264 refers to the transgenic AID gene that is a native gene, implies that the transgenic AID could either be such that the transgenic AID gene is an endogenous native AID gene that has had promoter regions regulated, but the actual AID gene itself is intact and undisturbed, therefore reading on "a transgenic AID gene;" or, it may imply that the transgenic AID gene is incorporated into a cell that already has a functional AID gene; OR the transgenic AID gene is incorporated into a cell that normally has a functional AID gene, but the native AID has been somehow disturbed, (supplementing an AID Knock Out cell with an AID transgene). On the other hand, if the methodology is referring to the mutated gene, the same situations mentioned above would have to be resolved according to which gene and which cell the gene is being mutated in. Thus a

skilled artisan would be unable to determine the metes and bounds of the claimed invention.

15. Claims 294-297 (and dependent claims 299 and 300) recite a change in affinity or specificity in a mutated antibody for "the antigen" of the antibody of the methodology of claim 125. Claim 125 recites a method of altering an affinity or a specificity of a monoclonal antibody to an antigen, or altering a cross reactivity of the monoclonal antibody to a second antigen... Thus claim 125 has two distinct antigens upon which mutations can be conferred (a first and a second). It is unclear to which antigen claims 294-297 are directed towards. If the method requires identification of the monoclonal antibody, one must be aware of where the mutations are directed towards. Mutations that effect affinity or specificity are not necessarily distinct from mutations that alter cross-reactivity. Thus a skilled artisan would be unable to determine the metes and bounds of the claimed invention.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 1-4, 6-9 13, 15, 19-22, 24-25, 58, 97, 125, 262--272, and 276-284, 287-288, 289-291, and 293-300 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wabl et al (US Patent No: 5,885,827) in view of Muramamatsu et al (Class Switch Recombination and Hypermutation require Activation-Induced Cytidine Deaminase (AID), a Potential RNA Editing Enzyme. Cell, 2000. 102:553-563).

19. Claims 1-5, 6-9,19-25, and 262-268 recite a method of inducing and identifying a mutation in a gene in a eukaryotic cell, wherein the gene is operably linked to a promoter, and wherein the gene is within about 2 kb of the promoter, the method comprising expressing a transgenic AID gene in the cell and expression the mutated gene in the cell, establishing and culturing clonal colonies of the cell; and identifying one or more clonal colonies that comprise a mutation in the gene (claim 1), wherein the gee is operably linked to an enhancer (claim 2) that is an immunoglobulin enhancer (claims 3) and wherein the gene is between 10 bases and 2 kb in the 3' direction from the promoter (claim 4), wherein the polyA mRNA of the gene ranges from 0.1% to 1% of total mRNA in the cell (claims 6-9). The method is further limited wherein the AID gene is flanked by a sequence foreign to the cell, wherein the sequence foreign to the cell is

at least 200 base pairs long (claim 13) or at least 2000 base pairs long (claim 15) wherein the cell is a vertebrate cell (claim 19), mammalian cell (claim 20) B cell (claim 21), a mammalian hybridoma (claim 22). The method is further limited wherein the gene is an antibody gene (claim 24) or wherein the gene encodes a protein selected from the group consisting of an enzyme, a transcription factor, a cytokine and a structural protein (claim 25). The method is further limited wherein the gene is integrated into the genome of the cell (claim 262), the gene is present extra-chromosomally in the cell (claim 263) or wherein the gene a native gene (claim 264). The method of claim 1 is further limited wherein the gene is a transgene (claim 265), and wherein the AID gene is constitutive (claim 266), inducible (claim 267), and under the control of a tet system (claim 268).

20. Claims 58, 269-272, 276-283, and 287-288 recite a method of inducing and identifying a mutation in an antibody gene in a eukaryotic cell, the method comprising expression a transgenic AID gene in the cell and expression the antibody gene in the cell, establishing and culturing clonal colonies of the cell, and identifying one or more clonal colonies that comprises a mutation in the antibody gene (claim 58). The method is further limited wherein the antibody gene encodes at least a portion of an antibody that binds to an antigen (claim 269), wherein the expression of the AID gene is constitutive (claim 270), wherein the AID gene is inducible (claim 271) under the control of a tet system (claim 272). The method is further limited wherein the antibody gene is selected from the group consisting of a human or humanized antibody, a mouse antibody, a rabbit antibody and a hamster antibody (claim 276). The method is further

limited wherein the mutated antibody gene has a higher affinity for the antigen (claim 277), a lower affinity for he antigen (claim 278) a higher specificity for the antigen (claim 279), a lower specificity for the antigen (claim 280), encodes a portion of an antibody that has altered cross-reactivity for the second antigen (claim 281) with an increased cross-reactivity (claim 282) or a decreased cross-reactivity (claim 283) that the antibody before the mutation, and that both the light chain and the heavy chain are mutated (claim 284). The method is further limited wherein the cell is a vertebrate cell (claim 287) or a mammalian cell (claim 288).

21. Claim 97 recites a method of inducing and identifying a class switch in an antibody heavy chain gene in a eukaryotic cell, the method comprising expression a transgenic AID gene in the cell and expressing the antibody heavy chain gene in the cell, establishing and culturing clonal colonies of the cell, and identifying one or more clonal colonies comprising the class switch in the antibody heavy chain gene.

22. Claim 125 and 289-291, 293-300 recites a method of altering an affinity or a specificity of a monoclonal antibody to an antigen, or altering a cross reactivity of the monoclonal antibody to a second antigen, wherein the monoclonal antibody is produced by a eukaryotic cell, and wherein the cell is capable of expressing a transgenic AID gene under inducible control, the method comprising (a) expressing the AID gene in the eukaryotic cell for a time and under conditions sufficient to induce a mutation in a gene encoding the monoclonal antibody; (b) suppressing expression of the AID gene in the eukaryotic cell (c) establishing clonal colonies of the cell; and (d) determining wherein the monoclonal antibody produced by any of the clonal colonies of the cell has altered

affinity or specificity to the antigen, or altered cross reactivity to the second antigen. The method is further limited wherein steps (a) through (d) are repeated with a clonal colony that has altered affinity or specificity to the antigen, or altered cross-reactivity to the second antigen (claim 289) wherein the clonal cells are enriched for cells producing high affinity antibodies by FACS (claim 290), wherein the inducible AID gene is under control of a tet system (claim 291) and wherein the AID gene is flanked by a sequence foreign to the cell, wherein the sequence foreign to the cell is at least 200 base pairs long (claim 292). The method is further limited wherein the monoclonal antibody is selected from the group consisting of a human or humanized antibody, a mouse antibody, a rabbit antibody, and a hamster antibody (claim 293). The method is further limited wherein the mutated monoclonal antibody gene has a higher affinity for the antigen (claim 294), a lower affinity for the antigen (claim 295) a higher specificity for the antigen (claim 296), a lower specificity for the antigen (claim 297), encodes a portion of an antibody that has altered cross-reactivity for the second antigen (claim 298) with an increased cross-reactivity (claim 299) or a decreased cross-reactivity (claim 300) that the antibody before the mutation.

23. These methods read on inducing methods of hypermutation on genes, including monoclonal antibodies, by overexpressing a cytidine deaminase AID transgene under a tet inducible system to regulate expression, and identifying cell clones expressing the mutated genes, as well as identifying the mutations based on changes to affinity or specificity of the mutated antibody.

24. Wabl et al (US Patent 5,885,827) teaches a method for performing saturation mutagenesis on a target gene by exploiting the immunoglobulin hypermutation system. A target gene is cloned into an expression vector containing immunoglobulin enhancer fragments that effect hypermutation, and this construct is then transfected into an immunoglobulin mutator cell, the target gene is permitted to hypermutate, and the mutated proteins are then selected (see abstract). He teaches that one use of this methodology can be directed towards in vitro affinity maturation of antibody genes (including human antibodies) for their ability to bind ligands and antigens (column 9, lines 40-53). He teaches that the gene to be mutated is operably linked to a promoter, and is within 2 kb of the promoter on the “hypermutation competent expression vector” which comprises immunoglobulin enhancer regions, and is within 2 kb in the 3’ direction of the promoter (column 2, lines 64- column 3 line 9, column 6, lines 31-51, column 6 line 66- column 7 line 31). Wabl teaches that the frequency of mutation occurs near the immunoglobulin variable region, and decreases drastically after about 2kb (5’ and 3’) from the region (column 2, lines 64- column 3 line 9). Wabl also teaches that other immunoglobulin genetic sequences can be present (column 6, lines 15-17).

25. Wabl teaches his method can be performed in a “mutator positive cell line” which he teaches is, “a cell line containing cellular factors that work in combination with enhancers to effectuate hypermutation. The cell line is preferably of pre-B lymphocyte origin, and more preferably of murine origin, or it can be a cell line transfected with factors determined to effectuate hypermutation” (column 8, lines 14-20). He teaches that the cDNA encoding the mutation factor can be transfected into the cell line (column

8, lines 20-40). The murine B cells of Wabl read on vertebrate cells. He further teaches that the mutator cells can be fused into hybridomas, thus producing monoclonal antibodies (see example 4), and mutants can be selected and isolated by establishing, and culturing and isolating stable cell lines (clonal colonies) (column 8, lines 14-40) or the clonal cells are enriched by using FACS analysis in order to determine the altered affinity of the antibodies (column 8, lines 41- column 9 lines 5).

26. Wabl teaches the method can be used to mutate erythropoietin (a cytokine) (column 10, lines 13-27). Wabl teaches that the mutator cell lines comprising the mutation expression vector can integrate into the genome of the cell, and that the mutation of antibodies in a b-cell includes the mutation of a native immunoglobulin heavy chain *Cμ* gene as a transgene located extra-chromosomally, wherein the endogenous *Cμ* gene was not mutated, but the transgene *Cμ* was mutated (see column 4, lines 29-52, and figure 2).

27. Wabl teaches that the hypermutation construct can be controlled by using a tetracycline regulating system including the tet promoter in order to induce or suppress expression (column 6, lines 26-29; example 5). Wabl further teaches that depending upon the situation, either constitutive or inducible promoters can be used in his system (Column 6, lines 14-29)..

28. Wabl does not teach that the altering of the antibody includes a class switch, or that the mutation factor capable of causing the hypermutation is an AID cysteine deaminase transgene, either constitutively expressed, or inducibly expressed while under the control of a tet promoter.

29.

30. Muramamatsu et al (Class Switch Recombination and Hypermutation require Activation-Induced Cytidine Deaminase (AID), a Potential RNA Editing Enzyme. Cell, 2000. 102:553-563) teaches that the AID gene is required for Class Switch Recombination (CSR) and Hypermutation in cells without induction by cytokines when over-expressed (see abstract).

31. Muramamatsu teaches:

32. To examine whether AID is involved in CSR, we transfected CH12F3-2 cells with the AID cDNA directed by an inducible tetracycline (tet) promoter. Three independent transfectants were examined for stimulation of class switching upon AID induction. We first confirmed that AID mRNA was in fact induced in the transfectants by the removal of tet (figure 1A). Endogenous AID mRNA was detectable only by RT-PCR without stimulation (data not shown). The transfectants were stimulated to switch from IgM to IgA with the suboptimal concentration of CD40L, IL-4, and TGF-beta (Figure 1B, right). Under these conditions, AID induction by the removal of tet enhanced class switching of CH12F3-2 cells 2-5 fold. It is worth noting that AID expression alone induced class switching significantly, albeit weakly, in CH12F3-2 cells (Figure 1B, left). There results provide gain-of-function evidence for the involvement of AID in class switching (page 556).

33. Muramamatsu teaches that AID mRNA is inherently present and thus constitutively expressed in b-cells of his experiments. Muramamatsu teaches that the AID transgene is flanked by a foreign expression vector with tet-response elements and IRES-EGFP segments, greater than 200 base pairs (see page 561). Considering the IRES-eGFP gene from Clontech is 1207 base pairs, and the entire IRES-eGFP vector from Clontech is 5 kb, absent evidence to the contrary, the AID transgene is flanked by at least 2000 base pairs. Muramamatsu teaches that the antibody heavy chains and light chains are mutated in heterozygous AID knockout mice, a result that is not seen in the AID knockout mice (page 558). Thus Muramamatsu concludes that AID cytidine

deaminase is a mutation factor capable of causing class switch recombination and hypermutation, and that an AID cytidine deaminase transgene under the control of a tet promoter is capable of directly causing class switch recombination in b-cells.

34. Because Wabl teaches that the mutation occurs within 2 kb of the variable region of in immunoglobulin enhancer region, and the specific mutations are inherently random within that region, and Muramamatsu teaches the over expression of AID, combined with the claimed method active steps in causing the mutations in the antibodies only includes expressing the AID transgene that is capable of increasing or decreasing affinity or specificity for an antigen, absent evidence to the contrary, a method which teaches the same steps would yield the same result to an antibody after expression of the AID transgene.

35. Neither Wabl nor Muramamatsu specifically teach that the mRNA of the AID transgene nor the mutated genes are calculated against the total mRNA concentration in the cell. However, both teach that calculation of mRNA is part of the methodology, and in northern analysis one often compares target mRNA to a housekeeping mRNA. MPEP 2144.05 teaches that generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Applicants have not shown that these mRNA concentrations are required for the success of the methodology of inducing mutations in

genes, and applicant teaches that the measurement of mRNA is simply to monitor transgene expression:

36. Any promoter or enhancer known in the art that allows the expression of the gone in the eukaryotic cell can be used for these methods. Preferably, the promoter allows moderate to high expression of the gene in the cell. The amount of expression can be measured by any means known in the art, including quantitative measurement of the gene product, or preferably quantitation of polyA mRNA. A useful measurement of gene expression of a particular gene is the determination of the relative amount of polyA mRNA of the gene compared to total mRNA in the cell. The skilled artisan can make this determination without undue experimentation using well-known methods. (page 15 of the instant specification).

37. Therefore, absent evidence to the contrary, the limitations of how much mRNA (0.1-1% mRNA) of the gene is in the cell compared to the total mRNA is not being weighted as anything other than routine optimization of a methodology.

38. It would have been obvious to the skilled artisan to combine the teaching of Wabl on a method of somatic hypermutation on immunoglobulin antibody or cytokines genes exploiting the immunoglobulin enhancer regions in b-cell monoclonal hybridoma colonies which already express factors necessary for somatic hypermutation, or are genetically induced to express a cDNA causing somatic mutation further with the teaching of Muramamatsu on the identification of a transgenic AID cytidine deaminase which is a mutation factor required for causing class switch recombination and hypermutation, and that an AID cysteine deaminase transgene under the control of a tet

promoter is capable of directly causing class switch recombination in b-cells, resulting in a method of inducing and identifying a mutation in a gene in a eukaryotic cell, wherein the gene is operably linked to a promoter, and wherein the gene is within about 2 kb of the promoter, the method comprising expressing a transgenic AID gene in the cell and expression the mutated gene in the cell, establishing and culturing clonal colonies of the cell, and identifying one or more clonal colonies that comprise a mutation in the gene.

39. All of the components of the claimed methods are known in the art (exploiting the immunoglobulin enhancer regions for causing somatic hypermutation in antibodies and endogenous genes, and over-expression of AID gene results in the hypermutation and class switch of antibodies), although not in a single reference. One of ordinary skill in the art could have combined the elements as claimed by known methods and that in combination, each element merely would have performed the same function as it did separately, and that one of ordinary skill in the art would have yielded the predictable result of inducing somatic hypermutation in immunoglobulin antibodies and identifying clones producing new monoclonal antibodies (see *KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007)*). Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

40. Claims 5, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wabl et al (US Patent No: 5,885,827) and in view of Muramamatsu et al (Class Switch Recombination and Hypermutation require Activation-Induced Cytidine

Deaminase (AID), a Potential RNA Editing Enzyme. Cell, 2000. 102:553-563) as applied to claims 1 above, further in view of in view of Wang et al (US Patent Publication 2003/0119190) (with priority to October 2001 via provisional application 60/327129). Claims 5 and 23 recite a method of inducing and identifying a mutation in a gene in a eukaryotic cell, wherein the gene is operably linked to a promoter, and wherein the gene is within about 2 kb of the promoter, the method comprising expressing a transgenic AID gene in the cell and expression the mutated gene in the cell, establishing and culturing clonal colonies of the cell, and identifying one or more clonal colonies that comprise a mutation in the gene, wherein the promoter is a immunoglobulin promoter, and the cell is a human cell.

41. Wabl and Muramamatsu teach a method of inducing and identifying a mutation in a gene in a eukaryotic cell, wherein the gene is operably linked to a promoter, and wherein the gene is within about 2 kb of the promoter, the method comprising expressing a transgenic AID gene in the cell and expression the mutated gene in the cell, establishing and culturing clonal colonies of the cell, and identifying one or more clonal colonies that comprise a mutation in the gene (see above). Neither Wabl nor Muramamatsu teaches that the promoter is an immunoglobulin promoter (claim 5), nor that the method is performed in a human cell (claim 23).

42. Wang et al (US Patent Publication 2003/0119190; with a priority date of October 3, 2001 to US provisional application 60/327,129) teaches a method for performing saturation mutagenesis on a target gene in an endogenous host cell genome by exploiting the immunoglobulin hypermutation system (see abstract). An expression

vector containing immunoglobulin enhancer fragments that effect hypermutation is then transfected into a vertebrate host cell, the construct comprising a cis-acting hypermutation element, wherein introducing of the construct provides for integration of at least the cis-acting hypermutation element into a host cell genome, and adjacent an endogenous host cell gene so that transcription of the endogenous host cell gene and the cis-acting hypermutation element facilitates introduction of a mutation into the endogenous host gene to generate a mutated gene (page 3, paragraph 0020). Wang teaches that one use of this methodology can be directed towards mutation of endogenous antibody genes (page 3, paragraph 0026). Wang teaches that the gene to be mutated is operably linked to a promoter, and is within 2 kb of the promoter on the "hypermutation competent expression vector" which comprises immunoglobulin enhancer regions, and is within 2 kb in the 3' direction of the promoter (page 5, paragraphs 0057-0061, and figure 2). Wang also teaches that other immunoglobulin genetic sequences can be present including the immunoglobulin Ig gene promoter (column 2, paragraph 0014). Additionally, Wang teaches that the construct can be extra-chromosomally in the cell, as an episomal element (paragraph 0069). Wang teaches that the host cell can be a human cell (page 10, paragraph 0103). Wang teaches the cell can be a cell line transfected with factors determined to effectuate hypermutation" (column 8, lines 14-20). He teaches that the cDNA encoding the mutation factor can be transfected into the cell line (column 8, lines 20-40).

43. Wang does not teach that the altering of the antibody includes a class switch, or that the mutation factor capable of causing the hypermutation is an AID cysteine

deaminase transgene, either constitutively expressed, or inducibly expressed while under the control of a tet promoter.

44. The US publication for Wang et al (US Patent Publication 2003/0119190; with a priority date of October 3, 2001 to US provisional application 60/327,129) teaches the expression of a mutation factor of AID cytidine deaminase in the cell. However, this teaching is NOT supported by the provisional application 60/327,129. **Thus, Wang does not teach the use of an AID transgene prior to the priority date of the instant application, and is NOT being used to supply this limitation into the rejection.**

45. It would have been obvious to combine the method of 1) Wabl and Mutamamatsu teach a method of inducing and identifying a mutation in an antibody gene in a eukaryotic cell, the method comprising expression a transgenic AID gene in the cell and expression the antibody gene in the cell, establishing and culturing clonal colonies of the cell, and identifying one or more clonal colonies that comprises a mutation in the antibody gene, as an improvement to somatic hypermutation seen in phage display libraries as their methodology resulted in much higher mutation rates , with the teaching of 2) Wang on methods of inducing mutations in antibody genes in human cells using immunoglobulin promoters because 3) as Wabl teaches mutating different types of antibodies was already known in the art using different cells and promoters, and one of skill in the art would have 4) recognized that the improved mutation rate due to the design of the method of Wabl and Mutamamatsu would result in a much higher number and quicker mutation of different antibody genes using native promoters in human cells, and could have been implemented into the method of Wabl and Mutamamatsu

successfully, predictably resulting in the mutation of antibody genes (see *KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007)*). Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

46.

47. Claims 273, 274, and 275 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wabl et al (US Patent No: 5,885,827) and Muramamatsu et al (Class Switch Recombination and Hypermutation require Activation-Induced Cytidine Deaminase (AID), a Potential RNA Editing Enzyme. Cell, 2000. 102:553-563) as applied to claim 58 above, and further in view of Griffiths (US Patent 5,885,827). Claims 273-275 recite a method of inducing and identifying a mutation in an antibody gene in a eukaryotic cell, the method comprising expressing a transgenic AID gene the antibody gene in the cell, establishing and culturing clonal colonies of the cell, and identifying one or more clonal colonies that comprises a mutation in the antibody gene wherein the antibody gene is a single chain antibody (claim 273) a multivalent antibody (claim 274) or a catalytic antibody (claim 275).

48. Wabl and Mutamamatsu teach a method of inducing and identifying a mutation in an antibody gene in a eukaryotic cell, the method comprising expression a transgenic AID gene in the cell and expression the antibody gene in the cell, establishing and culturing clonal colonies of the cell, and identifying one or more clonal colonies that comprises a mutation in the antibody gene. Wabl and Wang individually teach that their

methodologies of inducing mutations are superior to the phage display library systems known in the art and result in high mutation rates then previously reported (see individual introductions). Neither Wabl, nor Mutamamatsu specifically teach that the antibody gene encodes a single chain antibody, a multivalent antibody, nor a catalytic antibody.

49. Griffiths et al (US Patent 5,885,793) teaches method of producing antibodies or antibody fragments using phage display with some degree of somatic mutation (see abstract and column 4, lines 8-20). Griffiths teaches his technique allow for rapid isolation of binding specificities of different types of antibodies, including single chain, multivalent and catalytic antibodies (column 13, lines 3040, column 15, lines 35-58).

50. It would have been obvious to combine the method of 1) Wabl and Mutamamatsu teach a method of inducing and identifying a mutation in an antibody gene in a eukaryotic cell, the method comprising expression a transgenic AID gene in the cell and expression the antibody gene in the cell, establishing and culturing clonal colonies of the cell, and identifying one or more clonal colonies that comprises a mutation in the antibody gene, as an improvement to somatic hypermutation seen in phage display libraries as their methodology resulted in much higher mutation rates , with the teaching of 2) Griffiths on a method of mutating antibody genes for single chain, multivalent and catalytic antibodies using phage display because 3) as Griffiths teaches mutating different types of antibodies was already known in the art, and one of skill in the art would have 4) recognized that the improved mutation rate due to the design of the method of Wabl and Mutamamatsu would result in a much higher number and quicker

mutation of different antibody genes, and could have been implemented into the method of Wang and Wable and Mutamamatsu successfully, predictably resulting in the mutation of different types of antibody genes (see *KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007)*). Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

51. Claims 18, 285 and 286 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wabl et al (US Patent No: 5,885,827) and Muramamatsu et al (Class Switch Recombination and Hypermutation require Activation-Induced Cytidine Deaminase (AID), a Potential RNA Editing Enzyme. Cell, 2000. 102:553-563) as applied to claim1 above, and further in view of Honjo et al (US Patent 6,815,914). Claims 18, 285 and 286 recite a method of inducing and identifying a mutation in a gene in a eukaryotic cell wherein the gene is operably liked to a promoter, and wherein the gene is within about 2 kb or the promoter, the method comprising expressing a transgenic AID gene, in the cell, and expressing the gene in the cell, establishing and culturing clonal colonies of the cell and identifying one or more clonal colonies that comprise a mutation in the gene, where in the cell is a yeast cell (claims 18 and 285) or an insect cell (claim 286).

52. Wabl and Mutamamatsu teach a method of inducing and identifying a mutation in an antibody gene in a eukaryotic cell, the method comprising expression a transgenic AID gene in the cell and expression the antibody gene in the cell, establishing and

culturing clonal colonies of the cell, and identifying one or more clonal colonies that comprises a mutation in the antibody gene, wherein the expression of a AID transgene occurs in a variety of cells including human and murine b-cells, myeloma and hela cells, as well as bacterial cells (see above). However, neither Wabl nor Mutamamatsu teach that the methodology occurs in yeast or insect cells as host cells.

53. Honjo et al (US Patent 6,815,914) teaches methods of expressing AID transgenic cDNAs in eukaryotic cells including host cells of yeast, bacterial and insect cells, murine and human cells, including myeloma and hela cells (see abstract and column 19, lines 9-57; column 20 lines 29-47). Honjo further teaches that these host cells are common in the art for producing recombinant proteins (Column 30 line 50 – column 31 line 5; and Column 31 lines 40-55)

54. It would have been obvious to combine the method of 1) Wabl and Mutamamatsu teach a method of inducing and identifying a mutation in an antibody gene in a eukaryotic cell, the method comprising expression a transgenic AID gene in the cell and expression the antibody gene in the cell, establishing and culturing clonal colonies of the cell, and identifying one or more clonal colonies that comprises a mutation in the antibody gene, as an improvement to somatic hypermutation performed in a variety of cells with the method of 2) Honjo on a method of expressing transgene AID in a variety of host cells including yeast and insect cells because 3) as Honjo teaches using bacterial, yeast and insect cells for producing recombinant native and non-native proteins was already known in the art, and one of skill in the art would have 4) recognized that the design of using multiple types of host cells for producing

recombinant AID transgene would broaden the applicability of the method of mutagenesis designed by Wabl and Mutamamatsu, and could have been implemented into the method of Wabl and Mutamamatsu successfully, predictably resulting in the mutation of different types of antibody genes (see *KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007)*). Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

Conclusion

55. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Makar, Ph.D. whose telephone number is 571-272-4139. The examiner can normally be reached on 8AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Kam/08/15/07

/Daniel M. Sullivan/
Primary Examiner
Art Unit 1636